NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

PENTACHLOROPHENOL

(CAS NO. 87-86-5)

IN F344/N RATS

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

April 1999

NTP TR 483

NIH Publication No. 99-3973

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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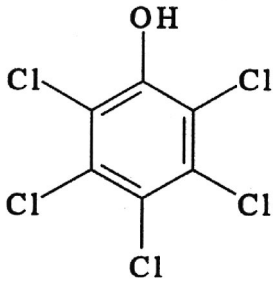
CONTENTS

ABSTRACT



PENTACHLOROPHENOL
CAS No. 87-86-5
Chemical Formula: CHOCl Molecular Weight: 266.3

Synonyms: Chlorophen; PCP; penchlorol; penta; pentachlorofenol; pentachlorofenolo; 2,3,4,5,6-pentachlorophenol

Trade names: Acutox; Chem-Penta; Chem-Tol; Cryptogil ol; Dowicide 7; Dowicide EC-7; Dow Pentachlorophenol DP-2 Antimicrobial; Durotox; EP 30; Fungifen; Fungol; Glazd Penta; Grundier Arbezol Lauxtol; Lauxtol A; Liroprem; Moosuran; Pentacon; Penta-Kil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-i-Trol; Thompson's Wood Fix; Weedone; Witophen P

Pentachlorophenol has been used as an herbicide, algicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. Pentachlorophenol was nominated by the National Cancer Institute for carcinogenicity testing based on its widespread use as a wood preservative, potential for entering the environment (pentachlorophenol residues have been found worldwide in soil, water, and air samples; in food products; and in human and animal tissues and body fluids), and likelihood of bioaccumulation in the environment (pentachlorophenol is persistent in soil, having a half-life of up to 5 years). Technical Report No. 349 contains the results of the 2-year studies of pentachlorophenol performed by the NTP with B6C3F mice.

Male and female F344/N rats were exposed to pentachlorophenol (approximately 99% pure) in feed for 28 days or 2 years. Genetic toxicology studies were conducted in vitro in Salmonella typhimurium and cultured Chinese hamster ovary cells and in vivo in rat and mouse bone marrow cells.

28-DAY STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were given 0, 200, 400, 800, 1,600, or 3,200 ppm pentachlorophenol, equivalent to average daily doses of approximately 20, 40, 75, 150, or 270 mg pentachlorophenol/kg body weight to males and females in feed for 28 days. With the exception of one male and two females exposed to 3,200 ppm, all rats survived until the end of the study. The final mean body weights and body weight gains of male rats exposed to 1,600 or 3,200 ppm and female rats exposed to 400, 800, 1,600, or 3,200 ppm were significantly less than those of the controls; rats exposed to 3,200 ppm lost weight during the study. Feed consumption by 3,200 ppm males was less than that by the control group throughout the study. The absolute and relative

liver weights of 400, 800, and 1,600 ppm males and all exposed groups of females were significantly greater than those of the controls. Compared to the control groups, the incidences of minimal to mild hepatocyte degeneration in males and females exposed to 400 ppm or greater and the incidences of centrilobular hepatocyte hypertrophy in the 3,200 ppm groups were increased.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were fed diets containing 200, 400, or 600 ppm pentachlorophenol (equivalent to average daily doses of approximately 10, 20, and 30 mg/kg) for 105 weeks. Stop-exposure groups of 60 male and 60 female rats received 1,000 ppm (equivalent to 60 mg/kg) in feed for 52 weeks, after which animals received undosed feed for the remainder of the 2-year study; 10 male and 10 female control and 1,000 ppm rats were evaluated at 7 months.

Survival, Body Weights, and Feed Consumption

In the 2-year study, survival of 600 and 1,000 ppm males was greater than that of the controls. Mean body weights of 400 and 600 ppm males and females were generally less than those of controls. When exposure to pentachlorophenol was discontinued at week 52, mean body weights of 1,000 ppm males and females were 17% and 22% lower than those of the respective controls; however, by the end of week 87, the mean body weights were similar to those of the controls. Generally, feed consumption by exposed groups was similar to that by the controls.

Pathology Findings

At 2 years, the incidence of malignant mesothelioma originating from the tunica vaginalis was significantly greater in 1,000 ppm males than in the controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 200 ppm males, one 400 ppm male, and five 1,000 ppm males at 2 years, and the incidence in 1,000 ppm males exceeded the historical control range. At the 7-month interim evaluation, the incidences of centrilobular hepatocyte hypertrophy in 1,000 ppm males and females and hepatocyte cytoplasmic vacuolization in 1,000 ppm males was significantly greater than those in the controls. At 2 years, the incidences of several nonneoplastic liver lesions including hepatodiaphragmatic nodules and hepatocyte cystic degeneration in all exposed groups of males and basophilic foci in 1,000 ppm males were increased compared to the controls.

GENETIC TOXICOLOGY

Pentachlorophenol (91.6% pure) was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 at doses up to 30 μg/plate with and without induced rat or hamster liver S9; no significant increases in the number of revertant colonies were observed in any of the strain/activation combinations. When tested for cytogenetic effects in cultured Chinese hamster ovary cells, pentachlorophenol was weakly positive for induction of sister chromatid exchanges and chromosomal aberrations. In the sister chromatid exchange test, a weakly positive response was observed within a concentration range of 3 to 30 μg/mL in the absence of S9; with S9, no induction of sister chromatid exchanges was noted. In the chromosomal aberrations test, pentachlorophenol was negative without S9 but induced small but significant increases in the frequency of aberrant cells in the presence of S9 at doses of 80 and 100 μg/mL. In contrast to the positive *in vitro* results in the test for induction of chromosomal aberrations, no increase in the frequency of micronucleated erythrocytes was noted in bone marrow of male rats or mice administered pentachlorophenol by intraperitoneal injection three times at 24 hour intervals. The highest dose administered to rats (75 mg/kg) and mice (150 mg/kg) was lethal.

CONCLUSIONS

Under the conditions of this 2-year feed study, there was *no evidence of carcinogenic activity** of pentachlorophenol in male or female F344/N rats fed diets containing 200, 400, or 600 ppm. There was *some evidence of carcinogenic activity* of pentachlorophenol in male F344/N rats given feed containing 1,000 ppm for 1 year followed by control feed for 1 year (stop-exposure study), based on increased incidences of mesothelioma and nasal squamous cell carcinoma. There was *no evidence of carcinogenic activity* of pentachlorophenol in female rats given feed containing 1,000 ppm for 1 year and maintained on control feed for 1 year.

Stop-exposure males and females recovered from a transitory reduction in body weight gain by the end of the 2-year study, and males had increased survival compared to the controls.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on pages 11 and 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pentachlorophenol

	Male F344/N Rats		Female F344/N Rats	
	(2-Year Study)	**(Stop-Exposure Study)**	**(2-Year Study)**	**(Stop-Exposure Study)**
Doses in feed	0, 200, 400, or 600 ppm	1,000 ppm for 1 year	0, 200, 400, or 600 ppm	1,000 ppm for 1 year
Body weights	400 and 600 ppm groups less than controls	Less than controls during exposure period; similar to controls postexposure	400 and 600 ppm groups less than controls	Less than controls during exposure period; similar to controls postexposure
Survival rates	12/50, 16/50, 21/50, 31/50	27/50	28/50, 33/50, 34/50, 28/50	28/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	Malignant mesothelioma: 1/50, 9/50 Nose: squamous cell carcinoma (1/50, 5/50)	None	None
Level of evidence of carcinogenic activity	No evidence	Some evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative for TA98, TA100, TA1535, and TA1537 with and without S9			
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; weakly positive without S9			
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Weakly positive with S9; negative without S9			
Micronucleated erythrocytes Mouse bone marrow *in vivo*:	Negative			
Rat bone marrow *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on pentachlorophenol on 10 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 10 December 1997, the draft Technical Report on the toxicology and carcinogenesis studies of pentachlorophenol received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of pentachlorophenol by discussing the uses of the chemical and the rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplasms and nonneoplastic lesions in male and female rats. Dr. Chhabra also reported the findings of the earlier bioassay of two technical grades of pentachlorophenol in B6C3F$_1$ mice. The proposed conclusions for the 2-year study were *some evidence of carcinogenic activity* in male F344/N rats and *no evidence of carcinogenic activity* of pentachlorophenol in female F344/N rats.

Dr. Belinsky, a principal reviewer, did not agree with the proposed conclusion for the male rats. He found the level of evidence for nasal lesions hard to justify, noting that the incidence of neoplasms was quite variable, with none reported at 600 ppm in the 2-year study. Dr. Belinsky questioned the effects an ongoing fungal infection would have had in facilitating that type of lesion. Dr. R.R. Maronpot, NIEHS, said that the highest rate of fungal infection was in the controls, and that among the animals that had squamous cell carcinomas, only one showed any evidence of fungal infection; thus, there appeared to be little or no relationship between fungal infection and neoplasms. Dr. Belinsky asked for clarification on the rationale for the stop study. Dr. Chhabra responded by first describing the rationale for the design of the study. The chemical had been shown previously to be a mouse liver carcinogen, and this finding was supported by data from a 28-day toxicity study; hence, the 2-year study was designed on the basis of this information. The reason for the stop-exposure study was to first determine if preneoplastic liver lesions would develop after 6 months of exposure; this was to have been followed by stop exposure and observance of the progression or regression of lesions for the next 6 months. Because only mild liver toxicity was observed at the interim sacrifice, it was decided that exposure would be continued for up to a year, after which animals would be placed on control feed for the second year.

Dr. Chatman, the second principal reviewer, did not agree with the proposed conclusion regarding the male rats. She said that the incidences of nasal neoplasms in the 2-year study were not statistically significant and did not show a dose-response relationship; also, exposed groups did not show increased incidences of defined preneoplastic lesions. Dr. J.K. Haseman, NIEHS, said that internal staff discussions explored the same issues, but because nasal neoplasms are so uncommon, the conclusion was warranted. Dr. Chatman also thought that the frequency of fungal nasal infections was an additional variable interfering with the interpretation of the findings, and she wondered if the animals were immunocompromised.

Dr. Fischer, the third principal reviewer, agreed with the proposed conclusions. She said that the active fungal infection might be a confounding variable. Dr. Fischer asked about levels of pentachlorophenol in the general food supply, for purposes of making comparisons with the levels fed to the animals. Dr. Chhabra responded that information on levels in food was available and that this would be added to the report. Dr. Fischer noted that the numbers of metastatic lesions were elevated in all of the treatment groups and wanted this fact to be addressed in the discussion. Dr. Haseman responded that the numbers of metastatic lesions were misleading because most of the metastatic lesions had different cells of origin, and two neoplasms metastasized to a number of different sites, with each counted as a different metastatic neoplasm.

Dr. Bus contended that the findings on the reduction of body weight gain in the 28-day study as well as information from the previous rat bioassay suggested that 600 ppm was close to the maximum tolerated dose (MTD), and thus the 1,000 ppm dose was far in excess of the MTD; hence, the classification described for the neoplasms did not seem right. Dr. Chatman responded that the 1,000 ppm group was in reality a different study. Dr. J. Russo commented that the mesothelioma findings were quite important and that

their significance should not be minimized. Dr. Goldsworthy inquired if there was any reason for males to be more sensitive than females with regard to the two neoplasm sites. Dr. Maronpot said that he would not expect any difference with respect to the nasal carcinomas; however, with regard to mesotheliomas, male Fischer rats have more spontaneous neoplasms at that site than females.

Dr. P. Lin, University of North Carolina at Chapel Hill, presented data from his research on the macromolecular binding and genotoxic effects of pentachlorophenol in tissues obtained from the interim sacrifice at 7 months in the 2-year NTP study. He said that their research with some mineral fibers indicated that free radical formation could be involved in the development of mesotheliomas. Their findings showed that in male rats exposed to 1,000 ppm, there was a twofold increase in DNA lesions in the kidney. If free radicals were involved in pentachlorophenol carcinogenesis, this would then explain the unusual dose-response relationship observed for the mesotheliomas in male rats.

Dr. B. Bernard, SRA International, representing the U.S. Pentachlorophenol Task Force, remarked that he would focus on the mesotheliomas in the epididymis and nasal neoplasms. He criticized the exposure concentrations, noting that these were based on the 28-day study and not on the 13-week studies, as is normally done. He stated that the 1,000 ppm groups were originally intended to be carried forward for 2 years, but that exposure had to be stopped after 1 year when it became obvious that survival would pose a problem. He suggested that for various reasons, including the lack of a dose response and the absence of neoplasms at the highest cumulative dose, the data supported *equivocal evidence of carcinogenic activity* at best. Dr. J.R. Bucher, NIEHS, stated that 1,000 ppm was always intended to be a stop-exposure concentration and the NTP design never included a 2-year exposure concentration at 1,000 ppm.

Dr. Belinsky moved that the Technical Report on pentachlorophenol, purified, be accepted with the revisions discussed and the conclusion as written for female rats, namely, *no evidence of carcinogenic activity*; and that the conclusion for male rats be changed to *equivocal evidence of carcinogenic activity*. Dr. Chatman seconded the motion. After some discussions suggesting that the conclusion statement for the standard 2-year study at 200, 400, and 600 ppm and the stop-exposure study at 1,000 ppm be treated separately, Dr. Belinsky made a substitute motion that "under the conditions of the study, there was *no evidence of carcinogenic activity* in male and female rats exposed for 2 years to feed containing 200, 400, or 600 ppm pentachlorophenol and that there was *some evidence of carcinogenic activity* in male rats and *no evidence of carcinogenic activity* in female rats exposed to feed containing 1,000 ppm pentachlorophenol for 1 year followed by control feed for another year." Dr. Chatman seconded the substitute motion. Dr. Bus moved to amend the second part of the motion to designate the stop-exposure study as an *inadequate study of carcinogenic activity*, based on the occurrence of significant toxicity well beyond classical MTD definitions. There being no second, the amendment was tabled. Dr. Belinsky's substitute motion was then accepted unanimously with eight votes.